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Editor's Note

Myocardial Infarction: Summary of the TIMI Trials

Remembering which "TIMI" trial is which has always been a problem for me, and I suspect it has been for others as well. Even the acronym "TIMI" has multiple meanings, namely, Thrombolysis In Myocardial Infarction, Thrombolysis in Myocardial Ischemia, and Thrombin Inhibition in Myocardial Ischemia. I thought a review of these trials might be of interest to readers of *Clinical Cardiology*.

What follows will summarize these trials in a repetitive format—that is, TIMI Trial Number, Drug/Procedure, Major Endpoint(s), and Results. I have also included the references for those trials that have been published or presented for those who wish to know study details.

TIMI 1[1]

Drug/Procedure: Intravenous (IV) streptokinase vs. IV recombinant tissue plasminogen activator (rtPA) in patients with acute myocardial infarction (AMI).

Major Endpoint: Coronary angiography to assess reperfusion at 90 min.

Results: Higher reperfusion rate with rtPA. TIMI grade 2 or 3 (60% for rtPA vs. 35% for streptokinase).

TIMI 2A[2]

Drug/Procedure: Immediate (2 h) percutaneous transluminal coronary angioplasty (PTCA) (195 patients) vs. delayed (18–48 h) PTCA or coronary artery bypass graft surgery (194 patients) in AMI patients treated with rtPA vs. clinically driven revascularization (197 patients).

Major Endpoint: Predischarge left ventricular ejection fraction.

Results: No advantage of immediate revascularization following rtPA compared with delayed or clinically driven revascularization. Ejection fraction averaged 49.3%

TIMI 2B[3]

Drug/Procedure: Immediate IV beta blockade (720 patients) vs. delayed (> 6 days) beta blockade (714 patients) after rtPA therapy for AMI.

Major Endpoints: Ventricular function, mortality.

Results: No difference in clinical outcome at 6 weeks or one year. Global left ventricular ejection fraction averaged 50.5%.

TIMI 3A[4]

Drug/Procedure: Heparin vs. heparin plus accelerated IV rtPA for unstable angina and non-Q-wave MI.

Major Endpoints: Coronary angiographic stenoses at 48 h and TIMI grade flow.

Results: IV rtPA augmented lysis of thrombi and relief of coronary narrowings better than heparin alone.

TIMI 3B[5,6]

Drugs/Procedure: rtPA vs. placebo as initial therapy in unstable angina/non-Q-wave MI and early revascularization vs. early conservative therapy (1,473 patients).

Major Endpoints: Death, MI, failure of initial therapy.

Results: No difference (54.2 vs. 55.5%) at 6 weeks. No difference at 1 year.

TIMI 4[7]

Drug/Procedure: rtPA vs. anisoylated plasminogen streptokinase activator complex (APSAC) vs. combination in 382 patients with AMI.

Major Endpoints: Coronary angiographic estimation of infarct-related artery patency and TIMI grade 3 flow at 90 min.

Results: Infarct-related artery patency and TIMI grade 3 flow: rtPA 60.2 %, APSAC 42.9%, combination 44.8%.

TIMI 5[8]

Drug/Procedure: Dose-ranging pilot trial of IV hirudin vs. heparin following rtPA and aspirin for AMI (246 patients).

Major Endpoints: TIMI grade 3 flow at 90 min and at 18 to 36 h without death or reinfarction.

Results: At 90 min TIMI grade 3 flow was present in 64.8% of hirudin-treated vs. 57.1% of heparin-treated patients (p = NS) Infarct artery patency was similar in the two groups. At 18 to 36 h, infarct-related artery patency was 97.8% in the hirudin group vs. 89.2% in the heparin group ($p = 0.01$).

TIMI 6[9]

Drug/Procedure: Hirudin vs. heparin in conjunction with streptokinase and aspirin in 193 patients with AMI.

Major Endpoints

Safety: Occurrence of major hemorrhage.

Efficacy: Composite unsatisfactory outcome—for example, death, nonfatal infarction, new onset heart failure, cardiogenic shock, or ejection fraction < 40%.

Results

Safety: Major hemorrhage similar between the heparin and hirudin groups.

Efficacy: Composite endpoint: No significant difference between any of the treatment groups for heparin and hirudin. Trend toward a lower composite endpoint with the higher dose of hirudin compared with the lowest.

TIMI 7[10]

Drug/Procedure: Dose-ranging of IV hirulog for patients with unstable angina. All patients received aspirin (410 patients).

Major Endpoints: Clinically unsatisfactory outcome (death, nonfatal MI, rapid clinical deterioration, recurrent ischemic pain at rest with electrocardiographic changes by 72 h).

Results: No difference in primary endpoints at different doses.

TIMI 8[11]

Drugs/Procedure: Hirulog vs. IV heparin in patients with unstable angina or non-Q-wave MI. Planned enrollment 5,300 patients.

Major Endpoints: Efficacy and safety.

Results: Trial discontinued for reasons unrelated to the drugs.

TIMI 9A[12]

Drug/Procedure: IV heparin to a target activated partial thromboplastin time (aPTT) of 60 to 90 s vs. IV hirudin (0.6 mg/kg bolus followed by infusion of 0.2 mg/kg /h for 96 h) following thrombolytic therapy (streptokinase or rtPA) in patients with AMI. Enrollment was 757 patients. All received aspirin.

Major Endpoints: Clinical, safety, and efficacy.

Results

Safety: Similar rates of hemorrhage. No superiority of hirudin over heparin. Study stopped because the incidence of hemorrhage was greater than expected in both treatment groups.

Efficacy: No difference in primary endpoints (death, MI, severe heart failure, or shock).

TIMI 9B[13]

Drug/Procedure: IV heparin to a target aPTT of 55–85 s vs. IV hirudin 0.1 mg/kg in bolus followed by 0.1 mg/kg/h in patients with AMI who were treated with streptokinase or rtPA. All 3,002 patients received aspirin.

Major Endpoints

Safety: Rate of hemorrhage.

Efficacy: Composite of death, MI, severe heart failure, and cardiogenic shock.

Results

Safety: Rate of hemorrhage was similar (5.3 vs 4.6%).

Efficacy: No difference (11.9 vs. 12.9%).

TIMI 10A[14]

Drug/Procedure: Dose-ranging of TNK-TPA given as a single bolus in 113 patients with AMI.

Major Endpoints: Coronary angiography at 90 min and hemorrhage.

Results: TIMI grade 3 flow at 90 min was achieved in 57 to 64% of patients at the 30 to 50 mg doses. Major hemorrhage was experienced by 6.2% patients; in 6 of 7 patients this occurred in a vascular access site.

TIMI 11A[15]

Drug/Procedure: A dose-ranging trial of enoxaparin in 630 patients with unstable angina or non-Q-wave MI. Dose tier 1 = 1.25 mg/kg. Dose tier 2 = 1.0 mg/kg.

Major Endpoints: Composite endpoints of death, nonfatal MI, recurrent ischemia through Day 14, and major bleeding.

Results: Composite endpoints occurred in 5.6 and 5.2% of patients in dose tiers 1 and 2, respectively. Major bleeding occurred in 6.5 and 1.9% of patients in dose tiers 1 and 2, respectively.

TIMI 12[16]

Drug/Procedure: Randomized trial of oral sibrafiban, a selective antagonist of the glycoprotein IIb/IIIa receptor, in patients after an acute coronary syndrome. In all, 329 patients were entered into a double-blind dose-ranging trial vs. aspirin for 28 days.

Major Endpoints: Safety, tolerability.

Results: Sibrafiban achieved effective long-term platelet inhibition with a clear dose response but a relatively high incidence of minor bleeding. Major hemorrhage was no different than in patients receiving aspirin but minor bleeding occurred more frequently with sibrafibran than with aspirin.

TIMI 13

Trial was never planned because of the fate of Apollo XIII (McCabe CH, personal communication).

TIMI 14[17]

Drug/Procedure: Comparison of front-loaded rtPA, three low doses of rtPA plus abciximab, low and usual doses of streptokinase plus abciximab, and abciximab alone (444 patients).

Major Endpoint: Incidence of TIMI grade 3 flow at 90 min.

Results: 52% in the rtPA-alone arm; 32% in the abciximab-alone arm; 53, 63, and 61% in the respective rtPA plus abciximab groups; and 42, 38, and 48% in the respective streptokinase plus abciximab groups. Bleeding was slightly increased with higher doses of streptokinase and abciximab.

Future TIMI Trials

The following TIMI trials are underway but no data are available at this time:

TIMI 15

Klerval (a GP IIb/IIIa-receptor blocker) administered intravenously and orally for 24–92 h in patients with acute coronary syndromes. This is a dose-ranging study.

TIMI 16

Orbofiban (an oral GP IIb/IIIa-receptor blocker) vs. placebo in patients with acute coronary sydromes. This trial carries the acronym OPUS.

TIMI 17

Lanoteplase (nPA): Single-bolus thrombolytic therapy vs. accelerated rtPA in patients with AMI. This trial carries the acronym INTIME II (Intravenous nPA for Treatment of Infarcting Myocardium Early).

TIMI 18

Tirofiban (oral GP IIb/IIIa-receptor blocker) in acute coronary syndromes (invasive vs. conservative therapy). This trial carries the acronym TACTICS.

A Final Comment

After going through this exercise, I think I prefer trial acronyms to trial numbers. It might be easier to remember what is what! A future editoral will summarize the TIMI trials as they are presented in the public forum.

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